The Examiner maintains the position that Isomura et al. teaches a bisphosphonate composition for oral administration with anti-bone resorption activity useful in treating metastatic osteocarcinoma. The Examiner acknowledges that Isomura et al. does not teach the specific claimed compound in the treatment of bone lesion associated with multiple myeloma and myeloma itself, nor the claimed effective dose.

However, the Examiner states that Shipman et al. teaches that bisphosphonates have anti-bone resorption activity, anti-tumor activity, apoptosis inducing activity, and may be useful in treating multiple myeloma. Thus, the Examiner maintains that one of ordinary skill in the art would have been motivated to optimize the dosage range and use the claimed bisphosphonate in a composition to treat multiple myeloma and bone lesions associated with multiple myeloma.

In response, Applicants respectfully assert that the present invention is not obvious over Isomura et al. in view of Shipman et al.

Shipman et al.

Although the Examiner asserts that Shipman et al. teaches that bisphosphonates (BP) have direct anti-tumor activities, Applicants respectfully disagree for the following reasons.

1. In the Abstract of Shipman et al., two facts are disclosed. First, recent studies have suggested that bisphosphonate treatment may result in an improvement in survival in some patients with multiple myeloma (MM). Second, BP can decrease cell proliferation and induce apoptosis in human myeloma cells *in vitro*.

As the reason for the improved survival, Shipman et al. contends that there may be a direct anti-tumor action, based of the *in vitro* activities of BP in addition to the indirect action via the osteoclast activity inhibition. However, this description is merely an inference by the authors

and, as will be described below, there is no disclosure of any evidence which confirms a direct anti-tumor activity in the living body (*in vivo*).

2. Illustrative examples of the increased survival of patients with MM are disclosed in Shipman et al. in Table 1 (page 131) and at page 132, col. 2. The contents of some of these references are as follows. The Reference No. indicated below corresponds to Reference Nos. used in Shipman et al.

Reference No. **37** (British J. of Haematology, 100:317-325 (1998))[1] and Reference No. **38** (New England J. of Medicine, 344:488-493 (1996)) disclose test results of the administration of clodronate or pamidronate, in addition to the administration of general carcinostatic agents, and reveal that the skeletal event was improved but there was no statistically significant difference in survival.

Reference No. **41** (International J. of Haematology, 101:280-286 (1994)) discloses test results of the administration of clodronate, in addition to the administration of general carcinostatic agents, and reveals that "Parenteral clodronate prophylaxis prolongs survival in MM, probably because it allows better control of bone disease and reduces deaths related to it" (see Abstract).

Reference No. **43** (J. of Clinical Oncology, 16:593-602, (1998)) discloses results of clinical tests on the administration of pamidronate, in addition to the administration of general carcinostatic agents, and describes that use thereof "may improve the survival of patients on salvage therapy."

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[1] Copies of each of the publications discussed herein are included herewith for the Examiner's review.

All of these references are the results of tests on the bone symptoms-improving action of BP, in addition to the chemotherapy-using, already existing carcinostatic agents, and there are no illustrative descriptions about the carcinostatic action by BP alone. Even in the case in which improvement in survival was found, only a description of the action of BP on bone disease is provided. There is no description which indicates a direct anti-tumor action.

Accordingly, the fact that BP by itself has a direct anti-tumor action in the living body cannot be anticipated or suggested from the fact of an improvement in survival in some patients with multiple myeloma.

3. The ability of BP to decrease cell proliferation and induce apoptosis in human myeloma cells *in vitro*, in particular, the *in vitro* myeloma cell apoptosis action of clodronate, pamidronate and YM175, is disclosed at page 133, col. 2 to page 135, col. 1, of Shipman et al. Pamidronate shows the apoptosis action at a concentration of 500 μM, and YM175 at 100 μM. However, it is not confirmed whether the *in vitro* results lead to the actual *in vivo* therapeutic effects.

In order to show anti-tumor actions in the living body, it is considered to be necessary that this apoptotic activity selectively acts on myeloma cells, and that these compounds achieve a high concentration of from 100 to 500 μM in cancer tissues of the living body at a clinical dose, but facts for supporting these points are not disclosed in the references.

Reference No. 50 (Leukemia 12:220-229 (1998)) is cited in Shipman et al. at page 134, col. 2 through page 135, col. The authors of this publication state that "Whether or not MM targets are uniquely sensitive to the apoptotic, cytotoxic and/or cytostatic effects of bisphosphonates is unclear" (page 226, col. 4). They further state that "A more relevant question

is whether these cytotoxic concentrations of Pamidronate or Zoledronate can be reached in treated patients. Certainly, peak serum concentrations are far below the required threshold but, owing to the singular skeletal distribution of administered bisphosphonates, marrow concentrations may be sufficient to inhibit growth of myeloma cells" (page 226, col. 5). Based on the disclosure of this publication, it is evident that the mechanism of *in vivo* anti-tumor action is merely an inference.

Accordingly, since there is no showing that the *in vitro* action of BP also occurs *in vivo*, the *in vivo* anti-tumor effect of Applicants' compounds cannot be taught by the disclosure of the *in vitro* apoptotic action of BP. That is, the *in vivo* anti-tumor effect is not obvious from the *in vitro* apoptosis action.

4. At page 135, col. 2, of Shipman et al., "ANTI-TUMOUR EFFECTS OF BISPHOSPHONATES *IN VIVO*" are described and the disclosures of several references are discussed. The contents of the main references are as follows.

Reference No. **51** (Investigational New Drugs, 6:155-167 (1988)). This publication discusses the anti-tumor activity of pamidronate (APD) in methylnitrosourea-induced mammary carcinoma of the rat. However, the authors do not disclose or suggest anti-tumor activity on multiple myeloma.

Reference No. **53** (Cancer, 55:1030-1040 (1985)). The authors of this reference state that "The growth pattern of the MM was not substantially influenced by the treatment, even though there was an indication that APD exerts some cytotoxic effect on the MM cells" (see Abstract). Further, it is stated that there is no change in the value of M-protein as a cancer marker (cf. Table 1 at page 1035). Also, there is a disclosure in col. 2 of the Results, at page 1032, stating that

anasarca, anemia and the like toxicity were found and caused death in the APD-high administration group, and that tumors were observed predominantly in bone marrow and hepatocytes.

Reference No. 54 (Cancer Research, 55:3551-3557 (1995)): The authors of this reference disclose that risedronate inhibited bone metastasis in breast cancer mice. However, there is a disclosure stating that risedronate does not inhibit metastasis in soft tissues surrounding bone and may not have direct anti-tumor action (see Abstract and page 3556, col. 3). In this connection, this reference does not disclose or suggest the action on multiple myeloma

None of these references shows that BP has the anti-tumor action on multiple myeloma *in vivo*, but rather, the latter two reports show contradictory findings. Accordingly, the anti-tumor action of BP on multiple myeloma is not obvious from the descriptions based on these references, but rather is "taught away".

5. As is described in the CONCLUSION on page 135 of Shipman et al., some BP have growth-inhibiting and apoptosis-inducing actions on myeloma cells *in vitro*, but whether or not they have direct anti-tumor action is not clear. Instead, it is only an interesting topic to be studied further, so that it is evident that this is not knowledge in which the authors themselves have confidence.

6. As described above, Shipman et al. and the references disclosed therein reveal no data which shows that BP has anti-tumor action in multiple myeloma patients. Though the *in vitro* data suggest it is a possibility, when the *in vivo* data in cited references are taken into consideration, negative information which "teaches away" from the present invention is reported in large numbers, and these facts should be considered to the same extent.

Based on the above, the Shipman et al. does not teach that "BPs have direct anti-tumor activities", but merely suggests a single possibility.

7. Accordingly, Shipman et al. merely gives a motivation to attempt application of BP compounds to the treatment of multiple myeloma at most, so that it is evident that the multiple myeloma treating action of compound A of the instant application cannot be obvious, even if Shipman et al. were to be combined with Isomura et al.

Isomura et al.

1. In the comments of the Examiner on Isomura et al. (page 3, lines 12-15, of the Office Action), the Examiner states that "Isomura et al. also teaches the oral dosage of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1 -bisphosphonic acid to be useful in inhibiting bone resorption to be 0.1 to 10 mg daily (See col. 7, line 7-19)."

Applicants respectfully submit that this interpretation is incorrect. The noted dosage is for non-oral administration and the dose for the oral administration is correctly described as generally from 1.0 mg to 1.0 g (= 1,000 mg)/day/adult for oral administration. Also, the oral dose disclosed in the Test Method (col. 9, lines 4 to 56) of said reference is 3 or 10 mg/kg (210 or 700 mg/day in the case of 70 kg adult). Contrary to this, the preferred oral dose of the instant invention is 1 to 20 mg, preferably 3 to 10 mg, which is a range of only a selected low dosage part among the quite broad dosage range disclosed in the reference.

Moreover, it is known that absorption of BP at the time of oral administration is generally poor. For example, British Journal of Haematology, 101:280-286 (1998), discloses that significant decrease in the bone symptoms by a known typical BP, pamidronate, was not found as a result of clinical tests by the oral administration of 300 mg/day, and the markedly low oral

absorption is mentioned as the reason therefor (cf. Summary). Also, it is known that a plurality of BPs, when orally administered, cause ulcers and the like side effects in digestive tracts at a high frequency, and a digestive tract disorder has been reported also for the pamidronate of said reference (cf. page 282, Table III).

As described in the foregoing, it is evident from Example 5 of the specification of the instant application that compound A of the instant invention shows therapeutic actions for bone lesions induced by multiple myeloma and further, for the multiple myeloma itself, by its oral administration of from 1 to 20 mg, preferably from 3 to 10 mg, which is a far lower dose than those of the already existing BPs, and its side effects on digestive tracts are also low.

Thus, the ideal information on a specified low dosage of compound A of the instant invention is not disclosed in the reference of Isomura et al. and not taught from the reference of Shipman et al.

Accordingly, the excellent effect of low dose compound A or a salt thereof in the therapeutic methods of the claims of the instant application is not obvious from either or both references.

Additional points

Although the Examiner contends that the Examples of the instant application are not sufficient for showing unexpected effects, Applicants assert that the unexpectedly superior effects of the invention of the instant application are sufficiently disclosed by these Examples as described in the following.

1. Bone resorption inhibitory activities of compound A of the instant application, and pamidronate and risedronate as already existing BPs, at 0.1 mg/kg single intravenous

injection, are disclosed in Example 1 of the specification. This is a test example showing efficacy of compound A at a low dosage and showing that it has a characteristic superior to other agents. Since the effectiveness at a low dosage means that the dosage can be decreased and side effects can be reduced, its clinical advantages are apparent.

2. Example 2 of the specification shows the bone density improving effects of compound A of the instant application by its low dosage oral administration. As is shown in Table I of Shipman et al., oral administration dosages of known BPs are high dosages of 5 mg/kg/day for etidronate and from 1,600 to 2,400 mg/day for clodronate. Also, as described in the foregoing, it has been reported that pamidronate does not show its effect by a clinical test of 300 mg/day oral administration and that BP has considerably low oral absorption and causes ulcers and the like side effects in digestive tracts at high frequency by its oral administration (British Journal of Haematology, 101:280-286 (1998)).

Accordingly, this Example of the instant application showing the effect by low dosage oral administration shows an excellent effect which cannot be expected from conventional techniques.

3. Example 4 of the specification clearly demonstrates that compound A of the instant application possesses anti-tumor action, together with bone symptoms-improving action, in multiple myeloma patients. Indeed, distinct reduction of a tumor marker M protein (lgD) was observed, in addition to good reduction of the bone marker, in a clinical case in which 3 mg/day of compound A alone was administered to multiple myeloma patients.

Although a large number of clinical tests have been carried out on BPs, there are no reports of clinical studies which show a direct carcinostatic action at the same clinical dose of BP

that improves bone symptoms. The fact that compound A of the instant application reduced the tumor marker together with the bone marker is an extremely superior effect which cannot be expected from the references.

4. In Example 5 of the specification, clinical test results of pamidronate are compared with clinical results of low-dosage oral administration of compound A. The administration mode (a 4-hour intravenous infusion every 4 weeks) and dosage (90 mg) of pamidronate are amounts which were judged suitable as the clinical dose from the viewpoint of its effect and safety and are now used in the clinical field.

This Example shows that compound A of the instant application has bone lesion-treating activity similar to or more than that of pamidronate by more convenient oral administration without causing side effects, which is a superior unexpected result from the references.

In conclusion, Shipman et al. does not teach "BPs have direct anti-tumor activities." Furthermore, the fact that compound A of the instant application simultaneously showed bone symptom-improving activity and direct anti-tumor action by clinical testing is clearly a superior, unexpected effect.

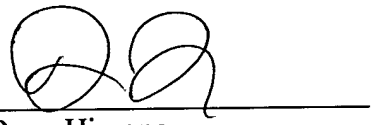
Accordingly, the treating method of the instant application using compound A, which has the ability to both treat multiple myeloma-induced bone lesions and treat multiple myeloma itself, is not obvious even assuming that Isomura et al. and Shipman et al could be combined. In addition, neither reference provides a motivation to select compound A of the instant application from the many BPs. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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